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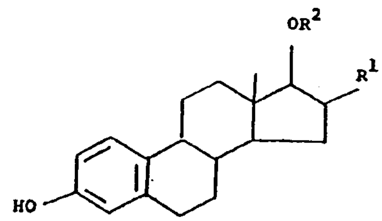
(54) ESTRADIOL DERIVATIVES

(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA, also known as TAKEDA CHEMICAL INDUSTRIES LTD., of 27 Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a body corporate organised under the laws of Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel and useful 16β-alkylestradiol derivatives and to a process for producing them.

More particularly, the present invention relates to 16β-alkylestradiols represented by the formula (I):



(I)

wherein R^1 is an alkyl group or an alkenyl group of two or more carbon atoms; and R^2 is hydrogen or an acyl group (as herein defined), and to a process for producing the compounds (I).

Hitherto, testosterone or derivatives thereof (e.g. testosterone propionate) have been introduced for the therapy of estrogen-dependent disease (e.g. advanced breast cancer) as antiestrogen drugs. However, the therapy is generally accompanied with the drawback *inter alia* that the virilizing effect resulting from the androgenic potency of testosterone prevents the patient from continuing with the therapy.

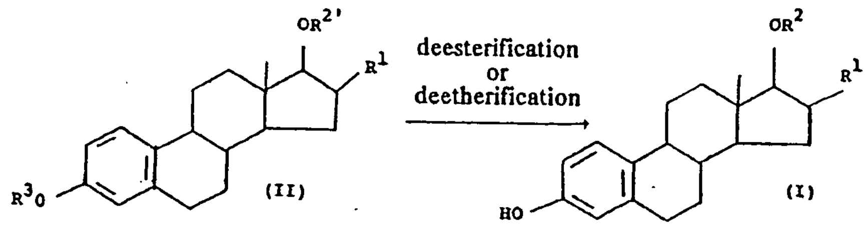
We have discovered that 16β-alkylestradiol derivatives have substantially no estrogen activity but rather have an antiestrogen activity, and that this propensity is particularly pronounced where the number of carbon atoms in the 16β-alkyl moiety is within the range of from 2 to 4. The present invention is accomplished on the basis of these findings.

The present invention provides compounds of the general formula (I), which are useful as an antiestrogen drug, and a process for producing the compounds (I).

Referring to the formula (I) and to formula (II) described below, the alkyl group or alkenyl group of two or more carbon atoms designated by R^1 may be straight-chain or branched, and saturated or unsaturated, thus being exemplified by lower alkyl groups having 2 to 4 carbon atoms, such as ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, allyl and 3-butenyl. The acyl group designated by R^2 in formula (I) above and by $R^{2\prime}$ and R^3 in formula (II) below is defined as a hydrocarbon-carbonyl group whose hydrocarbon moiety has from 1 to 8 carbon atoms. The hydrocarbon-carbonyl group is exemplified by lower alkylcarbonyl groups whose alkyl moieties have 1 to 3 carbon atoms, e.g. acetyl, propionyl, butyryl; arylcarbonyl groups, e.g. benzoyl; and aralkylcarbonyl groups, e.g. phenylpropionyl. Where R^2 and $R^{2\prime}$ are an acyl group, the substituent —OR^2 or —$OR^{2\prime}$ in the 17-position of formula (I) or (II) is an esterified hydroxyl group, and the corresponding compound is a 17-ester of the compound (I) or (II). The

hydrocarbon radical designated by R^3 in formula (II) is an alkyl, aryl or aralkyl group. The alkyl group mentioned for R^3 may be a straight-chain or branched lower alkyl group of 1 to 3 carbon atoms, viz. methyl, ethyl, propyl or isopropyl; the aryl group mentioned for R^3 may, for example, be phenyl or *p*-nitrophenyl; and the aralkyl group for R^3 may, for example, be benzyl or benzhydryl.

The compounds (I) of the present invention can be produced according to *per se* known methods. For example, the compounds (I) may be produced according to the method illustrated as follows:



wherin R^1 and R^2 have the same meaning as defined above, $R^{2'}$ is hydrogen or an acyl group, and R^3 is a hydrocarbon radical or an acyl group.

Thus, the above method is carried out by subjecting the compound (II) to a reaction leading to the cleavage of the acyl group or hydrocarbon radical of the esterified or etherified hydroxyl group in the 3-position thereof.

By the present reaction, the acyl group or hydrocarbon radical of the esterified or etherified hydroxyl group in the 3-position is removed, thus leaving a free hydroxyl group in the 3-position.

This reaction, where R^3 is an alkyl or aryl group, that is to say where $—OR^3$ is an etherified hydroxyl group, is carried out by reacting the compound (II) with a reagent capable of cleaving an ether linkage. The ether-cleaving reagent may be any reagent which is able to cleave the ether linkage of the etherified hydroxyl group in the 3-position without affecting the steroid skeleton and the 16β-alkyl group of the starting compound. Thus, for example, there may be mentioned acidic reagents, for example, hydrohalic acids such as hydrochloric acid, hydrobromic acid and hydroiodic acid, halides of phosphorus, boron, aluminium, thallium and titanium, preferably the corresponding chlorides and bromides (e.g. phosphorus tribromide, boron tribromide, aluminium chloride, titanium tetrachloride), pyridinium halides (e.g. pyridinium chloride); Grignard reagents (e.g. methylmagnesium iodide and ethylmagnesium bromide); and sodium iodide-dimethylsulfoxide. Generally, such ether-cleaving reagents are used in amounts within the range of from 1 to 10 moles per mole of the compound (II). While the reaction can take place in the absence of a solvent, it is generally carried out in the presence of a solvent. The solvent may be, for example an organic solvent capable of dissolving steroid compounds such as an ether (e.g. diethylether, tetrahydrofuran), a halogenated hydrocarbon (e.g. dichloromethane, chloroform, chlorobenzene, dichloroethane, trichloroethylene), an ester (e.g. ethyl acetate, butyl acetate), nitrobenzene, dimethylformamide, dimethylsulfoxide or hexamethylphosphoramide. The reaction is generally conducted within the temperature range of from −10°C. to 250°C. when no solvent is employed, or at a temperature within the range of from −10°C to the boiling point of the solvent when a solvent is employed. Following the reaction, the reaction mixture may be immediately treated with water to recover the desired compound. Where R^3 is an aralkyl group, the cleavage reaction according to this invention may be carried out by subjecting the compound (II) to catalytic reduction or hydrolysis. The catalytic reduction may be carried out in the presence of a catalyst such as platinum oxide, palladium or Raney nickel, generally in a solvent such as methanol, ethanol, ether or tetrahydrofuran at a temperature within the range of from 10°C to 60°C., and at a pressure within the range of from 1 to 100 kg/cm^2. Where R^1 is an unsaturated alkyl group, the conditions chosen should be such that the unsaturated bond will not be reduced, e.g. reduction at normal temperature and atmospheric pressure. The hydrolysis is carried out with the same reagent as the ether-cleavage reagent to be employed where R^3 is an alkyl or aryl group, or with a halogenoacetic acid such as trifluoroacetic acid, trichloroacetic acid or monochloroacetic acid under the same conditions as those employed for the ether-cleavage reaction where R^3 is an

alkyl or aryl group (e.g. as to the solvent, reaction temperature and other parameters).

Where R^3 is an acyl group, that is where $—OR^3$ is an esterified hydroxyl group, the cleavage reaction according to this invention may be carried out by subjecting the compound (II) to hydrolysis. This hydrolysis may be conducted by any procedure which enables cleavage of the ester linkage of the esterified hydroxyl group in the 3-position without affecting the steroid skeleton or the 16β-alkyl group of the starting compound (II). Thus, for example, the hydrolysis is generally conducted in a solvent. The solvent is a mixture of water and a solvent such as an alcohol (e.g. methanol, ethanol, *t*-butanol or *n*-propanol), ether, ethyl acetate, tetrahydrofuran, dimethylsulfoxide or dimethylformamide. The hydrolysis is conducted by means of an inorganic or organic basic reagent such as an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate), triethylamine or triethylenediamine, or an acid reagent such as an inorganic acid (e.g. hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid) or an organic acid (e.g. formic acid, acetic acid, oxalic acid, *p*-toluenesulfonic acid). The reaction is generally conducted at a temperature within the range of from 0°C. to substantially 80°C.

Where both the $R^{2'}$ and the R^3 groups of the starting compound (II) are acyl groups, both esterified hydroxyl groups in the 3- and 17-positions thereof are generally hydrolysed to free hydroxyl groups, but, if desired, the substituent in the 3-position of the compound (II) may be selectively hydrolysed to convert the esterified hydroxyl group in the 3-position alone to a free hydroxyl group by choosing a mild set of hydrolysing conditions, for example at a comparatively low temperature, e.g. room temperature, using a weakly basic reagent such as an alkali metal carbonate or alkali metal hydrogen carbonate.

Following the cleavage reaction of this invention, the contemplated end compound (I) may be isolated and purified by procedures which are conventional *per se* (e.g. treatment with water, extraction, concentration, recrystallization, chromatography).

The resulting compounds (I) have an antiestrogen activity, i.e. an inhibitory activity on the binding of estradiol to the estradiol-receptor protein isolated from the tissues of uterine, ovarian or breast carcinomas in mammals including mouse, rat and man, and have substantially no estrogen activity and no androgen activity. Further the present compounds (I) are low in toxicity, and therefore, are of use as antiestrogen drugs for the alleviation of highly estrogen-dependent diseases (e.g. functional uterine haemorrhage, mastitis, breast cancer, uterine cancer) in the said mammalian animals including mouse, rat and man.

Thus for example, the 16β-ethylestradiol has an antiestrogen activity which is several times as potent as that of clomiphene and testosterone, and can be used as an antiestrogen drug for the said mammals including mouse, rat and man in the same manner as testosterone is at present used for alleviation of the above diseases.

Compounds (I) except for 16β-ethylestradiol may also be employed, depending on the potency of their antiestrogen activity, as antiestrogen drugs in the same manner of usage as testosterone for the alleviation of the above diseases.

Where the compound (I) is employed as an antiestrogen drug, it may be orally or parenterally administered as it is, or in admixture with a known excipient or carrier (e.g. lactose, calcium phosphate, corn starch, methyl cellulose, coconut oil, sesame oil, peanut oil) in such dosage forms as tablets, capsules, powders, suspensions or injections.

These injections may be prepared, for example, by dissolving or suspending the compounds (I) in vegetable oils (e.g. sesame oil, cottonseed oil, castor oil, olive oil, corn oil, peanut oil) in combination, if desired, with antiseptics (e.g. benzyl alcohol, benzyl benzoate, chlorobutanol), solubilizing agents or surface-active agents. Among the compounds (I), 17β-ester derivatives are readily soluble in oils and exhibit a relatively sustained anti-estrogenic action. When the compounds (I) are administered orally, they may be administered as powders, tablets, capsules, pills, liquids, syrups, elixirs, buccals or granules. Some example of prescription in which the compounds of this invention are utilized as antiestrogen drugs are given below.

For example, where the compound (I) is administered parenterally as an antiestrogen drug for the alleviation of breast cancer, the intramuscular dose range is between 10 and 400 mg, more preferably between 30 and 100 mg, for an adult

female human per week. The dose may be divided into 2 to 3 weekly doses of the corresponding smaller amounts.

The compound (I) wherein R^2 is an acyl group, i.e. 17-ester of 16β-alkyl estradiol (I) is, generally speaking, long-active, slow-active, stable in storage and/or easy to prepare in dosage forms in comparison with the 17-hyroxyl compound corresponding thereto.

There may be exemplified compositions in which a compound of this invention is used as an antiestrogen drug;

Injections:

(1)	16β-ethylestradiol	10 weight parts
	sesame oil	1000 volume parts
(2)	16β-ethylestradiol 17-acetate	100 weight parts
	benzyl benzoate	20 volume parts
	sesame oil	1000 volume parts

Capsules:

16β-ethylestradiol 17-acetate	20 weight parts
lactose	140 weight parts
corn starch	50 weight parts
sugar ester	4 weight parts
calcium salt of carboxymethylcellulose	4 weight parts
magnesium stearate	2 weight parts
	(220 mg/capsule)

Tablets:

16β-ethylestradiol 17-acetate	20 weight parts
lactose	100 weight parts
corn starch	90 weight parts
sugar ester	4 weight parts
calcium salt of carboxymethylcellulose	4 weight parts
magnesium stearate	2 weight parts
	(220 mg/tablet)

In the prescriptions, "weight part" corresponds to "gram", and "volume part" corresponds to "milliliter".

The starting compound (II) for this invention may be produced by the method described in the specification of German Patent Application As Laid-Open No. 2100319.0 or by the method described in Chemical Pharmaceutical Bulletin Vol. 21, 1393 (1973), or a method analogous with the latter method, from the estra-1,3,5(10)-trien-16-oxo-17β-ols corresponding to the compound (II) or the compounds described in Tetrahedron Vol. 30, 2107 (1974). It should be noted that, generally, the estra-1,3,5(10)-trien-16-oxo-17β-ols or their derivatives may be produced by procedures similar to the procedures established for the species known among them.

The starting compound (II), wherein both $R^{2'}$ and R^3 are the same acyl group, can be produced by reacting the compound (I) wherein R^2 is hydrogen with an acylating agent according to *per se* known procedures established for the acylation of the alcoholic hydroxyl group. The acylating agent is exemplified by acid anhydrides (e.g. acetic anhydride, propionic anhydride, phenylpropionic anhydride)-organic or inorganic bases, acid halides (e.g. acetyl chloride, propionyl chloride, phenylpropionyl chloride, benzoyl chloride)-organic or inorganic bases, acids-dehydrating agents such as sulfuric acid, hydrochloric acid, dicyclohexylcarbodiimide. For example, the acylating reaction may be conducted in the presence of a catalyst which may be an alkaline catalyst such as, for example, pyridine, picoline, collidine, quinoline or a tertiary amine, e.g. triethylamine, or an acid catalyst such as, for example, a Lewis acid, e.g. boron trifluoride, zinc chloride or aluminium chloride, p-toluene sulfonic acid or potassium hydrogen sulfate. The

reaction is generally conducted in one of the common proton-inert solvents for steroids which include, among others, halogenated hydrocarbons, e.g. chloroform, dichloromethane, hydrocarbons, e.g. toluene, benzene, hexane, esters, e.g. ethyl acetate, dimethyl formamide, pyridine and picoline. Alternatively, use may be made of a large excess of the acylating agent such as an organic acid anhydride or the like so that the acylating agent will also function as the necessary solvent. The reaction usually proceeds at from 0°C. to room temperature, although the reaction may be hastened by heating the system to the neighborhood of 100°C. After the reaction is complete, the reaction mixture may, for example, be treated with a large quantity of water so as to let the acyloxy derivatives crystallize or, alternatively, be subjected to extraction with an organic solvent to recover the desired compound.

The invention is illustrated by the following examples:

Example 1

To 1 g of 16β-ethylestradiol 3-methyl ether are added 1.3 g of pyridinium chloride and the mixture is heated at 150°C. After 2 hours, the reaction mixture is poured into ice-water and the resulting crystals are collected by filtration. Recrystallized from ethyl acetate, 16β-ethylestradiol is obtained as needles melting at 173 to 174°C.

IR ν_{max}^{KBr} cm^{-1}: 3410, 3150 (OH, 1610, 1595 (Ar, "Ar" means "Aryl").

NMR $\delta_{ppm}^{d_6\text{-DMSO}}$: 0.68 (3H, s, 18-$CH_3$), 1.11 (3H, t, J=6Hz, CH_3), 3.57 (1H, d, J=9 Hz, 17α-H), 6.4—7.2 (3H, m, Ar).

Mass m/e 300 (M^+), 282, 213.

Elemental analysis, for $C_{20}H_{28}O_2$

Calcd.	C, 79.95;	H, 9.39
Found	C, 79.89;	H, 9.24

Example 2

To a solution of 2.3 g of 16β-ethylestradiol 3-methyl ether in 25 ml of ether is added an ethereal solution of solution of methylmagnesium iodide (prepared by reacting 1.2 g of magnesium with 7.0 g of methyl iodide in 50 ml of ether). The resulting mixture is gently heated and the ether is gradually removed under reflux. Following removal of the ether, the reaction mixture is further heated at 120°C for 2 hours. After cooling, the residue is carefully poured into ice-water in small portions. The aqueous mixture is adjusted to pH 2 with 5N-hydrochloric acid and the resulting crystals are collected by filtration. Recrystallized from ethyl acetate, 16β-ethylestradiol is obtained as needles. In melting point and IR spectrum, this product is in agreement with the product obtained in Example 1.

Example 3

In 10 ml of methanol are dissolved 360 mg of 16β-ethylestradiol 3,17-diacetate (melting point: 148 to 149°C), followed by the addition of a 2N-methanolic solution of potassium hydroxide. The mixture is heated at 50°C. for 3 hours. After cooling, water is added to the reaction mixture, and the resulting mixture is then adjusted to pH 2 with 5N-hydrochloric acid. The separated crystals are recovered by filtration to yield 16β-ethylestradiol. In melting point and IR spectrum, this compound is in agreement with the product obtained in Example 1.

Example 4

(1) To a solution of 0.17 g of 16β-ethylestradiol in 5 ml of pyridine is added 1 ml of acetic anhydride. After the resulting mixture has been kept at 50°C for 8 hours, 10 ml of water are added to the reaction mixture, and the mixture is extracted with dichloromethane. The organic layer is washed with water, dried over anhydrous sodium sulfate and concentrated, whereupon pale yellow crude crystals are obtained. Recrystallization from methanol gives 16β-ethylestradiol 3,17-diacetate as colourless needles melting at 148 to 149°C.

IR ν_{max}^{KBr} cm^{-1}: 1760 ($OCOCH_3$), 1725 ($OCOCH_3$).

(2) To a solution of 0.25 g of 16β-ethylestradiol 3,17-diacetate in 15 ml of methanol is added a solution of 19 mg of anhydrous potassium carbonate in 2 ml of methanol and the mixture is stirred at room temperature for 15 minutes. The

reaction mixture is concentrated under reduced pressure and made acidic with 2N-hydrochloric acid, whereupon crystals separate out.

Recrystallized from ether-*n*-hexane (1:1), 16β-ethylestradiol 17-acetate is obtained as colourless needles melting at 187 to 188°C.

IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1725 ($OCOCH_3$).

Elemental analysis, for $C_{22}H_{30}O_3$

Calcd.	C, 77.15;	H, 8.83
Found	C, 77.19;	H, 8.80

Example 5

(1) 16-Ketoestradiol 3-benzylether is reacted with ethyl magnesium iodide in ether to give 16β-hydroxyl-16α-ethylestradiol 3-benzylether. The product is treated with pyridine-acetic anhydride to give 16β-hydroxyl-16α-ethylestradiol 3-benzylether 17-acetate. The resulting 17-acetate is heated with zinc powder in toluene at 130°C for 5 hours to give 16β-ethylestrone 3-benzylether. The product is treated with sodium borohydride in methanol, whereupon 16β-ethylestradiol 3-benzylether is produced.

(2) In 30 ml of methanol is dissolved 0.73 g of 16β-ethylestradiol 3-benzylether, followed by the addition of 210 mg of platinum oxide. The catalytic reduction is thus conducted at atmospheric pressure and room temperature. After the absorption of hydrogen has been completed, the platinum oxide is filtered off and the filtrates are concentrated under reduced pressure. By the above procedure, 16β-ethylestradiol is obtained as crude crystals. This crude product is recrystallized from ethyl acetate as in Example 1. In melting point and IR spectrum, this product is in agreement with the product obtained in Example 1.

Example 6

To a solution of 0.93 g of 16β-isopropylestradiol 3-methyl ether in 15 ml of ether is added an ethereal solution of methylmagnesium iodide. The mixture is then treated in the same manner as Example 2, whereupon 16β-isopropylestradiol is obtained as crude crystals. The resulting crude crystals are recrystallized from ethyl acetate. Melting point: 221 to 222°C.

IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1610, 1590 (Ar).

NMR $\delta_{ppm}^{d_6\text{-}DMSO}$: 0.70 (3H, s, 18-$CH_3$), 0.83 (3H, d, J=5 Hz, CH_3), 0.98 (3H, d, J=5 Hz, CH_3), 3.73 (1H, d, J=9 Hz, 17α-H), 6.4—7.2 (3H, m, Ar)

Elemental analysis, for $C_{21}H_{30}O_2$

Calcd.	C, 80.21;	H, 9.62
Found	C, 80.30;	H, 9.67

Example 7

Under ice-cooling 0.2 g of phosphorus tribromide is added in small portions to a solution of 0.6 g of 16β-ethylestradiol 3-methyl ether in 10 ml of dichloromethane. The resulting mixture is allowed to stand at room temperature for 4 hours. The reaction mixture is poured in small portions into ice-water and extracted with dichloromethane. Upon removal of the solvent by concentration, 16β-ethylestradiol is obtained as crude crystals. Recrystallization under the same conditions as in Example 1 yields pure crystals. In melting point and IR spectrum, this product is in agreement with the product obtained in Example 1.

In a similar manner to the above, 16β-allylestradiol is obtained from 16β-allylestradiol 3-methyl ether. Melting point: 204 to 206°C.

IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 3080, 1640 (allyl), 1610, 1595 (Ar).

Elemental analysis, for $C_{21}H_{28}O_2$

Calcd.	C, 80.73;	H, 9.03
Found	C, 80.77;	H, 9.10

Example 8

(1) To a solution of 0.3 g of 16β-ethylestradiol in 2 ml of pyridine is added 0.6

ml of propionic anhydride. After keeping the resulting mixture at 50°C for 10 hours, 10 ml of water are added to the reaction mixture, followed by extraction with dichloromethane. The organic layer is washed with water, dried over anhydrous sodium sulfate and concentrated, whereupon crude crystals are obtained. Recrystallization from methanol gives 16β-ethylestradiol 3,17-dipropionate as colourless needles melting at 57°C.

IR ν_{max}^{KBr} cm^{-1}: 1760 ($OCOC_2H_5$), 1725 ($OCOC_2H_5$).

(2) To a solution of 0.2 g of 16β-ethylestradiol 3,17-dipropionate in 10 ml of methanol are added 16 mg of anhydrous potassium carbonate, followed by stirring at room temperature for 30 minutes. The reaction mixture is concentrated under reduced pressure, and the residue is made acidic with 2N-hydrochloric acid, whereupon crystals are obtained. The crystals are collected by filtration and recrystallized from hexane to give 16β-ethylestradiol 17-propionate as colourless needles melting at 176 to 178°C.

IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1700 ($OCOC_2H_5$).

Elemental analysis for $C_{23}H_{32}O_3$

Calcd.	C, 77.49;	H, 9.05
Found	C, 77.48;	H, 9.07

Example 9

(1) In a similar manner to Example 4-(1), 16β-isopropylestradiol 3,17-diacetate is obtained by acetylation of 16β-isopropylestradiol with acetic anhydride-pyridine. Melting point: 115 to 116°C.

IR ν_{max}^{KBr} cm^{-1}: 1765 ($OCOCH_3$), 1735 ($OCOCH_3$).

(2) In a similar manner to Example 4-(2), 16β-isopropylestradiol 3,17-diacetate is hydrolysed with anhydrous potassium carbonate to give 16β-isopropylestradiol 17-acetate. Melting point: 193 to 194°C.

IR ν_{max}^{KBr} cm^{-1}: 1350 (OH), 1700 ($OCOCH_3$).

Elemental analysis for $C_{23}H_{32}O_3$

Calc.	C, 77.49;	H, 9.05
Found	C, 77.31;	H, 9.11

Example 10

(1) To a solution of 0.2 g of 16β-ethylestradiol 3-methyl ether 17-acetate in 10 ml of dimethylsulfoxide is added 0.5 g of dried sodium iodide, and the mixture is refluxed for 3 hours under a nitrogen gas stream. After cooling, 30 ml of water are added to the reaction mixture, and the resulting mixture is extracted with ether. The ether layer is washed with water, dried over anhydrous sodium sulfate and concentrated, whereupon pale yellow crude crystals are obtained. Recrystallization from ether-hexane (1:1) gives 16β-ethylestradiol 17-acetate. This product is in accordance with the product obtained in Example 4 in melting point and IR spectrum.

(2) Similarly to Example 7, 16β-ethylestradiol 3-methylether 17-acetate is treated with phosphorus tribromide to yield 16β-ethylestradiol 17-acetate.

Example 11

(1) To a solution of 0.3 g of 16β-ethylestradiol in 10 ml of pyridine is added 0.5 g of 3-phenylpropionyl chloride, and the mixture is kept at room temperature for 12 hours. 10 ml of ice-water are added to the reaction mixture and the mixture is extracted with ether. The ether layer is washed with a 3N-aqueous solution of potassium carbonate, dried over anhydrous sodium sulfate and concentrated, whereupon 16β-ethylestradiol 3,17-diphenylpropionate is obtained.

IR ν_{max}^{Neat} cm^{-1}: 1760, 1735 ($OCOCH_2CH_2$—C_6H_5).

(2) To a solution of the product obtained in the above experiment (1) in 10 ml of methanol is added 0.1 g of potassium carbonate and the mixture is stirred at

room temperature for 30 minutes. The reaction mixture is concentrated, and to the resulting residue are added 10 ml of water, followed by extraction with ether. The ether layer is washed with water, dried over anhydrous sodium sulfate and concentrated, whereupon a crude oily product is obtained. The product is subjected to silica gel column chromatography using benzene-ether (3:1) as an eluent thereof to give 16β-ethylestradiol 17-phenylpropionate as a colourless oil.

IR ν_{max}^{Neat} cm^{-1}: 3400 (OH), 1700 ($OCOCH_2CH_2C_6H_5$), 1605 (Ar).

Mass: m/e 432 (M^+, M=432 for $C_{29}H_{36}O_3$) 404 (−29), 299 (−133).

Example 12

(1) In a similar manner to Example 11-(1), 16β-ethylestradiol is reacted with benzoyl chloride to give crude crystals. Recrystallization from ether gives 16β-ethylestradiol 3,17-dibenzoate melting at 177 to 178°C.

IR ν_{max}^{KBr} cm^{-1}: 1735, 1720 ($OCOC_6H_5$).

(2) According to a similar manner to Example 11-(2), 16β-ethylestradiol 3,17-dibenzoate is hydrolysed with potassium carbonate to give 16β-ethylestradiol 17-benzoate melting at 194 to 196°C.

IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1695 ($OCOC_6H_5$).

Elemental analysis for $C_{27}H_{32}O_3$

Calcd.	C, 80.16;	H, 7.97
Found	C, 79.87;	H, 7.99

Example 13

(1) 16-Ketoestradiol 3-methylether is reacted with *n*-butylmagnesium iodide to give 16β-hydroxy-16α-n-butylestradiol:

IR ν_{max}^{Neat} cm^{-1}: 3500 (OH), 1605, 1590 (Ar).

Acetylation of the compound with acetic anhydride in pyridine gives the corresponding 17-acetate:

IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1730 ($OCOCH_3$), 1605, 1595 (Ar).

The 17-acetate is treated with zinc powder in toluene for 4 hours at 130°C to give 16β-butylestrone 3-methylether:

IR ν_{max}^{Neat} cm^{-1}: 1735 (c=o), 1605, 1595 (Ar).

Reduction of 16β-butylestrone 3-methyl ether with sodium borohydride in methanol gives 16β-*n*-butylestradiol 3-methylether:

IR ν_{max}^{Neat} cm^{-1}: 3500 (OH), 1605, 1595 (Ar).

In a similar procedure to the above experiment (1), 16β-(3-butenyl)-estradiol 3-methylether is produced from 16-ketoestradiol 3-methylether and 3-butenylmagnesium bromide.

IR ν_{max}^{Neat} cm^{-1}: 3500 (OH), 1635 (c=c), 1605, 1590 (Ar).

Mass: m/e 340 (M^+), 325 (−15), 322 (−18).

(2) In a similar manner to Example 2, 16β-*n*-butylestradiol 3-methylether is reacted with methylmagnesium iodide to give 16β-*n*-butylestradiol melting at 148 to 150°C (recrystallization from hexane).

IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1605 (Ar).

Elemental analysis for $C_{22}H_{32}O_2$

Calcd.	C, 80.44;	H, 9.83
Found	C, 80.40;	H, 9.99

In a similar manner to the above experiment (2), 16β-(3-butenyl)-estradiol is obtained from 16β-(3-butenyl)estradiol 3-methylether.

Melting point: 154 to 156°C.

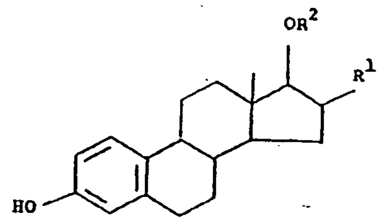
IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3050, 1635 (c=c), 1605 (Ar).

Elemental analysis for $C_{22}H_{30}O_2$

Calcd.	C, 80.93;	H, 9.26
Found	C, 80.62;	H, 9.58

WHAT WE CLAIM IS:—

1. A compound of the formula (I):



(I)

wherein R^1 is an alkyl group or an alkenyl group of two or more carbon atoms, and R^2 is hydrogen or an acyl group (as herein defined).

2. A compound as claimed in Claim 1, wherein the alkyl group represented by R^1 is a lower alkyl group having 2 to 4 carbon atoms.

3. A compound as claimed in Claim 1 or 2, wherein R^2 is hydrogen.

4. A compound as claimed in Claim 1 or 2, wherein R^2 is an acyl group.

5. A compound as claimed in Claim 4, wherein the acyl group represented by R^2 is lower alkylcarbonyl whose alkyl moiety is alkyl having 1 to 3 carbon atoms, benzoyl or phenylpropionyl.

6. 16β-ethylestradiol.

7. 16β-ethylestradiol 17-acetate.

8. 16β-isopropylestradiol.

9. 16β-allylestradiol.

10. 16β-ethylestradiol 17-propionate.

11. 16β-isopropylestradiol 17-acetate.

12. 16β-ethylestradiol 17-phenylpropionate.

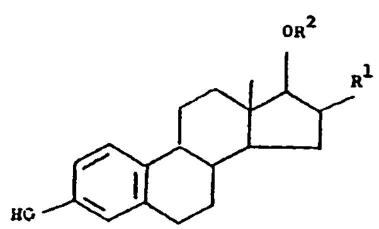
13. 16β-ethylestradiol 17-benzoate.

14. 16β-*n*-butylestradiol.

15. 16β-(3-butenyl)-estradiol.

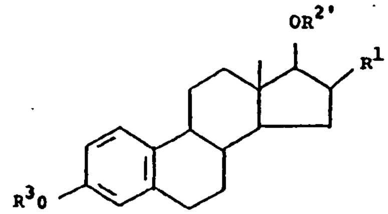
16. A pharmaceutical composition comprising any one of the compounds claimed in Claims 1 to 15, together with a pharmaceutically acceptable carrier or diluent therefor.

17. A process for producing a compound of the formula (I)



(I)

wherein R^1 is an alkyl group or an alkenyl group of two or more carbon atoms, and R^2 is hydrogen or an acyl group (as herein defined), which process comprises subjecting a compound of the formula (II):



(II)

wherein R^1 has the same meaning as defined above, $R^{2'}$ is hydrogen or an acyl group (as herein defined and R^3 is a hydrocarbon radical or an acyl group (as herein defined), to cleavage of the acyl group or hydrocarbon radical of the etherified or esterified hydroxyl group in the 3-position thereof.

18. A process as claimed in Claim 17, wherein R^3 is an acyl group.

19. A process as claimed in Claim 17, wherein R^3 is a hydrocarbon radical.

20. A process as claimed in Claim 19, wherein the hydrocarbon radical represented by R^3 is lower alkyl having 1 to 3 carbon atoms, phenyl, *p*-nitrophenyl, benzyl or benzhydryl.

21. A process as claimed in Claim 18, wherein the acyl group represented by R^3 is lower alkylcarbonyl whose alkyl moiety is alkyl having 1 to 3 carbon atoms, or arylcarbonyl.

22. A process for producing a compound (I) as defined in Claim 1, substantially as herein described with reference to any of the specific examples.

23. Compound (I) as defined in Claim 1 when produced by a process as claimed in any of Claims 17 to 22.

24. A pharmaceutical composition comprising at least one compound (I) as claimed in Claim 23, together with a pharmaceutically acceptable carrier or diluent therefor.

ELKINGTON & FIFE,
Chartered Patent Agents,
52—54 High Holborn,
High Holborn House,
London WC1V 6SH.
Agents for the Applicants.

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